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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
09/080,140	05/15/98	BILLING-MEDEL	P	6105.US.P1

HM12/1017

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EXAMINER	
CANELLA,K	
ART UNIT	**PAPER NUMBER**
1642	16

DATE MAILED: 10/17/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary

Application No.	Applicant(s)
09/080,140	Billing-Medel et al
Examiner	**Group Art Unit**
Karen Canella	1642

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3 months* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *10-16, 25, 30, 33, 35, 38, and 39* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *10-16, 25, 30, 33, 35, 38, and 39* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

Response to Amendment

1. Please note that the examiner assigned to your application in the PTO has changed.
2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
3. Claims 10, 11, 14, 15, 25, 30, 33, 38 and 39 are amended. Claims 10-16, 25, 30, 33, 35, 38-39 are under consideration.

New Rejections

4. Claims 38 and 39 are rejected under 35 U.S.C.101 as the claimed invention is directed to non-statutory subject matter. Claims 38 and 39 are respectively drawn to polynucleotides which code for a protein and polynucleotides comprising DNA. As such both claims read on polynucleotides that exist in situ and are therefore non-patentable materials.

5. Claims 10-16, 25, 30, 33, 35, and 38-39 are rejected under 35 U.S.C. 112, second paragraph.

Claims 10, 11, 15, 25, 33, 38 and 39 recite "identity". Without reference to the specific algorithm used to calculate the percent identity, the metes and bounds of the claims cannot be determined.

Claims 10-16, 25, 30, 33, 35, and 38-39 are rejected under 35 U.S.C. 112, second paragraph, because they do not conform to the Sequence Rules which specify that all references to polynucleotide or polypeptide sequences in the specification or in the claims should be labeled with a "SEQ ID NO:" identifier. Claims 10, 11, 15, 25, 30, 33, 38 and 39 recite "SEQUENCE ID NO". Correction to --SEQ ID NO:-- is required.

6. Claims 10-16, 25, 30, 33, 35 and 38-39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The disclosed use of polynucleotides encoding PS116 consisting of polynucleotides having at least 70% identity to SEQ ID NO:1-12, and compositions of matter thereof, and kits containing polynucleotides encoding PS116 consisting of polynucleotides having at least 70% identity to SEQ ID NO:1-12, and methods for producing polypeptides comprising polypeptides having at least 70% identity to SEQ ID NO:25-29 and polynucleotides encoding polypeptides having at least 70% identity to SEQ ID NO:25-29 is the detection of prostrate cancer. The specification teaches that EST sequences were obtained from prostate tumor libraries. From this collection EST sequences were selected that were represented primarily in prostate tumor tissue, and a consensus sequence (a contig of overlapping clones) was generated. However, the data presented in the specification is not enabling for the use of these sequences in the detection of prostate cancer. The specification states on pg. 55, lines 1-2, that the EST corresponding to the consensus sequence of PS116 were detecting in less than half of the prostate tissue libraries surveyed. Analysis of actual clinical samples by Northern Blot (Figure 3) indicates that 2 out of 6 samples of RNA from normal prostate hybridized with the labeled PS116 probe and all five samples of RNA from prostate cancer tissue failed to hybridize with the PS116 probe. Table 1 on pg. 62 indicates the results of a ribonuclease protection assay using PS116 RNA. PS116 RNA was found to be expressed at 22 pg in a single sample of bladder cancer per micorgram of RNA and 8 pg in a single sample of normal prostate cancer per microgram DNA. The specification teaches the raising of an antiserum to the polypeptide of SEQ ID NO:27. The specification used this antiserum in a the resulting Western Blot of protein from normal bladder, cancerous bladder, colon, lung, breast, normal prostate, and prostate cancer. However, the results do not support the usefulness of PS116 in the detection of prostate cancer: one out of three samples of bladder cancer and one out of three prostate cancer samples were positive when labeled with the antiserum raised against SEQ ID NO:27. From the evidence given in the specification, there is no

statistically significant evidence correlating the expression of SEQ ID NO:1-12 with prostate cancer. Because of all the above, one of skill in the art would not be able to practice the claimed invention with a reasonable expectation of success.

7. In the event that Applicants might be able to overcome the 35 USC 112 rejection above, the specification would still be enabling only for claims limited to polynucleotides consisting of SEQ ID NO:1-12, polynucleotides that encode the amino acid sequences SEQ ID NO:25-29 and a method of producing a polypeptide comprising SEQ ID NO:25-29 because the specification does not reasonably provide enablement for polynucleotide variants having at least 70% identity to SEQ ID NO:1-12, polynucleotides that encode polypeptide variants comprising amino acid sequences having at least 70% identity to SEQ ID NO:25-29, expression systems comprising polynucleotides having at least 70% identity to SEQ ID NO:1-12, methods for producing a polypeptide comprising one epitope or polypeptides encoding an epitope or epitopes of PS116. The specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

The instant claims encompass polynucleotides comprising non-disclosed nucleic acid sequences which are at least 70% identical to SEQ ID NO:1-12 and polynucleotides that encode the amino acids that are 70% identical to the polynucleotides of SEQ ID NO:25-29. As disclosed above, the specification does not teach how to use the polynucleotides of SEQ ID NO:1-12 or the polynucleotides that encode SEQ ID NO:25-29, therefore, since the specification has not taught how to use said polynucleotides, the specification has not enabled the scope of claims drawn to polynucleotides having 70% identity to SEQ ID NO:1-12 and polynucleotides which encode polypeptides having 70% identity to SEQ ID NO:25-29. When given the broadest reasonable interpretation, the claims are clearly intended to encompass a variety of species including full-length cDNAs, genes and protein coding regions. Clearly, it would be expected that a substantial number of the polynucleotides encompassed by the claims would not share either

structural or functional properties with polynucleotides that encode SEQ ID NO:25-29 or encode proteins that share either structural or functional properties with PS116. The specification fails to provide an enabling disclosure for how one would use such variant polynucleotides encoding variant polypeptides. Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Clearly, with 30% dissimilarity, to SEQ ID NO:25-29 the function of the variant polypeptides could not be predicted, based on sequence similarity with SEQ ID NO:25-29, nor would it be expected to be the same as that of SEQ ID NO:25-29.Clearly, given the teachings of Bowie et al,

Lazar et al, and Burgess et al, with a 30% dissimilarity, to SEQ ID NO:25-29, the function of the could not be predicted. Further, even if the polypeptides having at least 70% identity to SEQ ID NO:25-29 are PS116 polypeptide, neither the specification nor any art of record teaches the statistically significant correlation to prostate cancer or establish any involvement of the PS116 polypeptide in the etiology of prostate cancer. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art on how to use the broadly claimed species. For the above reasons, undue experimentation would be required to practice the claimed invention.

8. Claims 14, 25, and 30 are drawn to polynucleotides comprising sequences which encode at least one epitope.. The instant specification defines epitope (pg. 15, lines 37-38) as "the antigenic determinant of a polypeptide". Roitt (Immunology Textbook) defines epitope as "A single antigenic determinant....the portion of the antigen which combines with the paratope of the antibody." The specification does not list or give examples of amino acid residues which would constitute an epitope or epitopes of SEQ ID NO:25-29.

Paul (Fundamental Immunology, 3rd Edition, pg. 251, column 1, lines 11-12) states that immunogenicity is limited by self-tolerance, and that the repertoire of potential antigenic sites in a given polypeptide is a specific for the host organism. Klein ("Self-nonself discrimination, histoincompatibility, and the concept of immunology", Immunogenetics, 1999, Vol. 50, No. 3-4, pp. 116-123) teaches that the property of immunogenicity for a polypeptide is based upon the recognition of said polypeptide as a "non-self" polypeptide. Ristori et al (FASEB, 2000, Vol. 14, No. 3, pp. 431-438) have disclosed that the discrimination between self and non-self proteins do not rely on simple qualitative features of the amino acid sequences in question, and that foreign, "non-self" peptides, known not to be present in humans, can mimic "self" antigens and thus can be tolerated (non-immunogenic) within the host. Therefore, it would be difficult to predict what

peptides an "epitope" would consist of having only the amino acid sequence of the polypeptides SEQ ID NO:25-29.

Paul also teaches (supra, pg. 249, column 2, lines 10-13) that to determine the immunogenicity of certain regions of a protein, knowledge of the three dimensional structure of the protein is required to determine which polypeptides in a given protein would be accessible on the surface of the protein in order for the putative antigenic determinant to be bound by the antibody. In addition, Paul states that mobility of the putative antigenic determinant within the native protein structure is also a determining factor for the binding of the antigenic determinant to an antibody. Paul points out (supra, pg. 250, lines 4-8) that "Measurement of the mobility in the native protein is largely dependent on the availability of a high resolution crystal structure, so its applicability is limited to only a small subset of proteins." The determination of an "epitope" is clearly a non-trivial enterprise, and without further guidance from the specification on known sequences of the PS116 polypeptide which have been determined to be epitopes in a specific organism, it would require undue experimentation for one of skill in the art to make and use the invention as claimed.

9. Claims 10-16, 25, 30, 33, 35 and 38-39 are rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case only sets forth SEQ ID NO:1-12, polynucleotide sequences encoding the amino acid sequences of SEQ ID NO:25-29 and therefore the written description is not commensurate in scope with the claims drawn to polynucleotide variants wherein the variants are polynucleotides having at least 70% identity to SEQ ID NO:1-12 and polynucleotides encoding polypeptides comprising amino acid sequences having at least 70% identity to SEQ ID NO:25-29, and polynucleotides encoding epitopes.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed. (See page 1117). The specification does not clearly allow persons of ordinary skill in the art to recognize that the applicant invented what is claimed. (See Vas-Cath at page 1116).

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Reiger et al (Glossary of Genetics and Cytogenetics, Classical and Molecular, 4th Ed., Springer-Verlag, Berlin, 1976) clearly define alleles as one of two or more alternative forms of a gene occupying the same locus on a particular chromosome..... and differing from other alleles of that locus at one or more mutational sites (page 17). Thus, the structure of naturally occurring allelic sequences are not defined. With the exception of SEQ ID NO:4, the skilled artisan cannot envision the detailed structure of the encompassed polynucleotides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid itself is required. See Fiers V. Revel, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Lts., 18 USPQ2d 1016.

Furthermore, In The Reagents of the University of California v. Eli Lilly (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that an adequate written description of a DNA...requires a

precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention. No disclosure, beyond the mere mention of polynucleotides having at least 70% identity to SEQ ID NO:1-12 is made in the specification. This is insufficient to support the generic claims as provided by the Interim Written Description Guidelines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

Therefore only an isolated DNA molecule consisting of SEQ ID NO:1-12 and a polynucleotide sequence encoding the polypeptides of SEQ ID NO:25-29, and equivalent degenerative codon sequences thereof, but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph.

10. All other rejections and objections cited in Paper No. 12 are withdrawn.

Conclusion

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

GEETHA P. BANSAL
PRIMARY EXAMINER

Karen A. Canella, Ph.D.
Patent Examiner, Group 1642
October 13, 2000